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REVIEW

Blood—brain barrier breakdown-inducing astrocytic transformation: Novel targets for the prevention of epilepsy

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Summary Epileptogenesis is common following brain insults such as trauma, ischemia and infection. However, the mechanisms underlying injury-related epileptogenesis remain unknown. Recent studies demonstrated impaired integrity of the blood—brain barrier (BBB) during epileptogenesis. Here we review accumulating experimental evidence supporting the potential involvement of primary BBB lesion in epileptogenesis. Data from animal experiments demonstrate that primary breakdown of the BBB prone animals to develop focal neocortical epilepsy that is followed by neuronal loss and impaired functions. The extravasation of albumin from the circulation into the brain neuropil was found to be sufficient for the induction of epileptogenesis. Albumin binds to transforming growth factor β receptor 2 (TGFβR2) in astrocytes and induces rapid transcriptional modifications, astrocytic transformation and dysfunction. We highlight a novel cascade of events which is initiated by increased BBB permeability, eventually leading to neuronal dysfunction, epilepsy and cell loss. We review potential mechanisms and existing experimental evidence for the important role of astrocytes and the TGFβ pathway in epileptogenesis. Finally, we review evidence from human clinical data supporting the involvement of BBB lesion in epilepsy. We propose that primary vascular injury, and specifically BBB breakdown and repair, are key elements in altered interactions within the neurovascular unit and thus may serve as new therapeutic targets.

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Contents

Injury-related epileptogenesis: a potential role for blood—brain barrier disruption and serum-derived albumin

Focal epilepsy typically arises from neuronal tissue either within or adjacent to a cortical lesion (Willoughby, 2000). The focus of epileptic tissue is often located in the hippocampal formation within the temporal lobe (temporal lobe epilepsy, TLE). Neurosurgical removal of the epileptogenic area in many patients leads to control or even abolishment of seizures. However, in light of the high rate of drug resistant focal epilepsies, and other neurological impairments following insults to the central nervous system, novel anti-epileptogenic strategies are urgently needed.

Epileptiform activity can be experimentally induced by a number of drugs which block potassium currents, augment sodium currents or impair synaptic inhibition (Opdam et al., 2002; Prince, 1969). Long-lasting or persistent focal neocortical epilepsies can be elicited by inducing developmental cortical malformations via trauma early in life (Jacobs et al., 1996), repeated electrical stimulation such as in the kindling model of epileptogenesis (McNamara, 1986) or repeated application of ictogenic agents, such as penicillin (Opdam et al., 2002; Prince and Wilder, 1967) or pentetrazole (Barkai et al., 1990), by focal application of epileptic agents (Opdam et al., 2002; Prince and Wilder, 1967), or by chronic injury to, or the deafferentation of the adult cerebral cortex (Halpern, 1972; Pitkanen and McIntosh, 2006; Prince and Tseng, 1993). The most frequently used animal models for TLE depend on the induction of status-epilepticus (SE) by systemic injection of pilocarpine or kainic acid (for review see Curia et al., 2008). In most of these animal models (similar to the situation in man), a period of days to weeks is required for the development of epileptic activity (Hoffman et al., 1994; Prince and Tseng, 1993). Typically, the transient insult is followed by a latent interval in which cellular and structural reorganization processes occur, referred to as *epileptogenesis*, which ultimately leads to chronic recurrent epileptic seizures. While the molecular, anatomical and electrophysiological activity in the epileptic brain focus have been described in great details (see for example Hoffman et al., 1994; Huguenard et al., 1996; Jacobs et al., 1999; Prince and Futamachi, 1968; Prince and Tseng, 1993; Mody and Heinemann, 1987; Prince and Gutnick, 1971), the changes that are critical to epileptogenesis, occurring following injury and before epileptic activity develops — are mostly unknown. An understanding of the molecular and physiological events during epileptogenesis is essential for the targeted development of preventive therapeutic approaches that are presently unavailable (Herman, 2002).

On the basis of clinical and animal studies, accumulating evidence support the hypothesis that primary vascular lesions and, specifically an opening of the blood—brain barrier (BBB), trigger a chain of events leading to epilepsy (Avivi et al., 2004; Ivens et al., 2007; Janigro, 1999; Marchi et al., 2007; Oby and Janigro, 2006; Pavlovsky et al., 2005; Seiffert et al., 2004; Tomkins et al., 2007, 2008; van Vliet et al., 2007). It is noteworthy that a significant and long-lasting BBB breakdown is a hallmark of cortical injury (Cervos-Navarro and Lafuente, 1991; Tomkins et al., 2008; Tomkins et al., 2001). Moreover, ultrastructural studies on human epileptic tissue show clear BBB abnormalities, including increased micropinocytosis and fewer mitochondria in endothelial cells, a thickening of the basal membrane, and the presence of abnormal tight junctions (Cornford, 1999; Cornford and Oldendorf, 1986; Kasantikul et al., 1983). Recently, a role for BBB opening in the progression of TLE was suggested based on the finding of positive immunocytochemistry to albumin following SE and a positive correlation between the extent of BBB opening and the number of seizures (van Vliet et al., 2007). While large amount of published data support a correlation between epileptogenesis, seizures and abnormal BBB, direct evidence for the involvement of BBB breakdown in epileptogenesis has been only recently given by a series of studies in which we demonstrated that in a rat model, a long-lasting opening of the BBB (using focal application of bile salts (Greenwood et al., 1991) indeed results in the delayed appearance of robust hypersynchronous epileptiform activity (Seiffert et al., 2004). Importantly, BBB disruption does not seem to induce epileptogenesis by provoking status epileptogenesis, seizures or neuronal death. Although Marchi and co-workers showed that BBB disruption can provoke seizures in pigs (Marchi et al., 2007), it may not be to the same extent in naïve rodents although it does reduce seizure threshold in epileptic animals (van Vliet et al., 2007). Either way, epileptogenesis in the BBB-disrupted brain seems to be mediated by exposure of the brain cortex to serum albumin, mediated via its action on brain astrocytes (Ivens et al., 2007 and see below). The possible involvement of albumin in astrocytic activation and proliferation is supported by previous studies showing serum albumin inducing proliferation of fibroblasts (Tigyi et al., 1995) as well as calcium signaling and DNA synthesis in cultured astrocytes (Nadal et al., 1995). Based on their studies, Nadal and co-workers (1995) concluded that there is a specific receptor and signaling pathway for the action of albumin. While albumin is the most abundant protein in the serum, other blood-born proteins may also have a role in the epileptogenic process. For example, it has been recently shown that the serum protein, thrombin, acting through the protease-activated receptor 1 (PAR1), lowers the threshold